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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,784	BJORN ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-21* is/are pending in the application.

4a) Of the above claim(s) *10, 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6,8,9,11,12,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Office Action mailed February 25, 2004 has been vacated in favor of the following.

2. Applicant's response to the Office Action mailed June 17, 2003 on December 3, 2003 is acknowledged.

Claim Disposition

3. Claim 7 has been canceled. Claims 1-2 have been amended. Claims 1-6 and 8-21 are pending. Claims 1-6, 8-9, 11-12 and 20-21 (SEQ ID NO: 4) are under examination.

Claim Objection

4. Claim 3 is objected to because *Aequorea victoria,* the art recognized spelling, is misspelled as *Aequoria victorea* (see for example page 1 of the instant specification).

Appropriate correction is required.

5. The following grounds of rejection are or remain applicable:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6, 8-9, 11-12 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a modified form of an *Aequorea* GFP protein, however, no structure is provided in the claims to which the modification will occur (see for example, claims 1, 3-6, 8-9, 11-12 and 20-21), as the claims do not recite a specific sequence. Thus, the claims encompass a genus of molecules described by function only. The claims recite open language therefore, the claims encompass any structure as long as said structure comprises the above mutation and any functional analogue of an undefined structure. Additionally, the specification fails to describe or provide any identifying characteristics or properties of the analogue or provides data to demonstrate that function is retained, even for the sequences recited in claims 2 and 9-10 (SEQ ID NOS: 4 and 8). Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

7. Claims 1-6, 8-9, 11-12 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified GFP comprising the amino acid sequence set forth in SEQ ID NOS: 4 and 8 (claims 2 and 9-10) wherein the mutations are only at positions 64 (position 1 preceding the chromophore) and 222, does not reasonably provide enablement for a modified *Aequorea* GFP and any functional analogue of an unspecified structure with mutations at position 1 preceding the chromophore and position 222 as recited in claims 1, 3-6, 8-

9, 11-12 and 20-21. The specification is also not enabled for functional analogue of the sequences set forth above. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Factors considered in determining whether undue experimentation is required, are summarized in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Circ. 1988). They include but are not limited to: quantity of experimentation, the amount of direction or guidance presented, the presence or absence of working example, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and breath of the claims. The factors will be discussed below.

The claims are directed to any modified *Aequorea* GFP and any functional analogue (see for example claim 1). The specification does not describe/provide a structure or any characteristics of the claimed analogue, and is not enabled for any analogue. The term "analogue" does not have an art recognized definition, therefore, one of skill in the art would have to perform undue experimentation to determine what analogues of GFP and determine if said analogues retained the claimed biological function. Due to the large quantity of experimentation necessary to generate the infinite number of analogues of GFP recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The specification sets forth that the claimed protein is contained in SEQ ID NOS: 4 and 8, however, the claims broadly read on any structure as none is set forth in claim 1. The specification does not provide support for the broad scope of the claims, which encompass all modifications and any analogues of any GFP sequence that comprises a mutation at position 1 preceding the chromophore and

position 222. Therefore, absent direction/guidance regarding the structure that can tolerate the modifications and the analogues of GFP that will produce an excitation maximum at a higher wavelength and an increased fluorescence as set forth in the instant specification, thus, one of skill in the art would not have been able to practice the claimed invention commensurate in scope with the claims.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure. Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). Therefore, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship.

In addition, claim 12 broadly read on any kinase/cytoskeletal element, which is not supported by the disclosure in the instant specification, and the working examples provided do not demonstrate this embodiment.

In view of the foregoing, one of skill in the art would require guidance, beyond that provided in the instant specification, in order to make a modified GFP and GFP analogues comprising the mutation recited in claim 1 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 1-6, 8-9, 11-12 and 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the claim recites, "wherein the amino acid in position 1 preceding the chromophore has been substituted" and there is no indicia of what the substitution is to define the claimed structure. Note that the claim describes a substitution at position 222 only. Claim 1 is also indefinite because the claim does not presently recite the structure of the GFP protein that is to undergo the recited modifications, thus the claim is not complete. The claim recites positions to be altered without reference to a SEQ ID NO: and it is unclear what sequence is to be used as the reference sequence. The claim is also indefinite because it is directed to a fluorescent product "derived" from a modified form of a wild type GFP, however, the metes and bounds of the term "derived" are not defined neither in the specification nor the art,

rendering the claim unclear as there is no limitation on the number of changes in the wild-type structure that can occur. The term "functional analogue" is indefinite because the specification does not provide a definition that is limiting and there is no art-accepted definition, furthermore, no structure is provided in the claim. The recitation of substitutions at position 1 preceding the chromophore and at position 222 " renders the claim indefinite because it is unclear what structure is being modified and what modifications can be tolerated in the structure as they are undefined. The chromophore is also undefined as it is well known in the art that mutations can occur in the chromophore and the chromophore recited in the claim is not necessarily native, for example it could be a red shifted chromophore. In addition, there are many GFPs. The dependent claims hereto are also included in this rejection.

Basis For NonStatutory Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-6, 8-9, 11-12 and 20-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/296,953. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to a fluorescent protein derived from GFP or any functional analogue, wherein the amino acid in position 1 preceding the chromophore has been substituted and wherein the glutamic acid in position 222 has been substituted by amino acid selected from the group consisting of G, A, V, L and I (see claim 1 of the instant application) and the copending application has claims directed to the same protein consisting of an improvement which is that the mutated GFP has an excitation maximum at a higher wavelength and the fluorescence is increased when the mutated GFP is expressed in cells incubated at a temperature of 30 degrees or above compared to the wild-type GFP. Note that the instant application claims are a genus of the copending claims and that the improvement is inherent based on the same recited mutations. In addition the dependent claims for example claim 2 of the instant application and claim 8 of the copending application disclose the same protein structure.

The residues to be substituted are also identical in both applications. Note also that the GFP is derived from *A. victorea or Renilla* in each applications. Although the scope of the current claims differ, the two sets of claims are directed to the same subject matter. Thus, the instant application claim is an obvious variation of the copending application claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

12. Claims 1-6 and 8 remain rejected under 35 U.S.C. 103 (a) as being unpatentable over Thastrup et al. (WO 97/11094 March 27, 1997) in view of Ehrig et al. (FEBS Letters, vol. 367, pages 163-166, 1995).

Thastrup et al. teach a fluorescent protein derived from GFP (Aequorea green fluorescent protein) or any functional analogue thereof wherein the amino acid in position 1 preceding the chromophore has been mutated to provide an increase of fluorescence intensity. Thastrup et al. teach that the proteins exhibit high fluorescence in cells expressing them when said cells are incubated at a temperature of 30 degrees or above. Thastrup et al. also teach that the chromophore is in position 65-67 and the substitution of F at position 64 for an aliphatic amino acid (see pages 1-4, claims 1-4 of the instant application). Thastrup et al. teach that the preferred mutation is F64L (claims 5-6), however, deletions, substitutions, insertions or posttranslational modifications immediately preceding the chromophore are also included in the invention, however is silent on the E222G mutation recited in claim 1 of the instant specification. However, Ehrig et al. teach the E222G mutation (see abstract, claims 1 and 8). Ehrig et al. teach a single amino acid change producing a mutant of GFP (E22G).

Therefore, it would have obvious for one of ordinary skill in the art at the time the invention was made to modify the teachings of Thastrup et al. (GFP mutation F64L) by

adding in the teachings of Ehrig et al. (GFP E222G) to arrive at the claimed invention as a whole. One of ordinary skill in the art would be motivated to combine the teachings of the references because Thastrup et al., disclose that other mutations are possible preceding the chromophore provided that they result in improved fluorescence properties of the various fluorescent proteins (page 4, lines 10-15) and Ehrig teach such a mutation. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

13. The response filed on December 3, 2003 has been considered. The rejections of record have been maintained. Note however, that the rejection of record under 35 U.S.C. 112, second paragraph has been clarified with respect to the structure of the protein needed in the claim. In addition, although applicant amended the claims to recite "substituted" in lieu of "mutated", the structure remains undefined as there is no indication of what residues will be substituted. Claim 1 to be definite requires the recitation of a sequence for the GFP and the specific substitutions that can be tolerated by this sequence at the position 1 preceding the chromophore.

Note that art rejection remains. Applicant's response states that the claimed invention involves a combination of the F64L and E222G mutations of GFP. However, this argument is not convincing as the combined teaching of the references renders the invention as obvious. The rejection under 35 USC 103 above is consistent with case law. Applicants are referred to *In re Kerkoven* (205 USPQ 1069) in which it was shown to be *prima facia* obvious to combine two compositions, each of which is taught by the

prior art to be used for that very same purpose. *Ex Parte Quadranti* (25 USPQ2d 1071) also sets forth this precedent, in that the use of materials in combination, each of which is known to function for the intended purpose, is generally held to be *prima facia* obvious. *Ex parte Kucera* (165 USPQ 332) clearly states that synergism has no magical status in rendering otherwise obvious subject matter patentable. Therefore, then, barring unexpected results, one would reasonably expect enhanced, additive, or synergistic activity to be observed by combining the compositions or materials.

Applicant also states that the claimed invention results in an excitation of 470 nm compared to 481nm disclosed in Ehrig et al. This argument is not convincing because the claims do not recite the stated excitation maximum as a limitation to the claims. As stated above Ehrig et al. rectifies the silent teaching of Thastrup et al. with regard to the point mutation found at E222 and teaches the substitution of E to G, thus rendering obvious the claimed invention.

Conclusion

14. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER